(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 December 2002 (27.12.2002)

PCT

(10) International Publication Number
WO 02/102785 A1

(51) International Patent Classification[7]: C07D 261/12, 413/04, A61K 31/42, A61P 31/04

(21) International Application Number: PCT/US01/42943

(22) International Filing Date:
14 November 2001 (14.11.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/249,551 17 November 2000 (17.11.2000) US

(71) Applicant *(for all designated States except US)*: **PHARMACIA & UPJOHN COMPANY** [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GENIN, Michael, J.** [US/US]; 33303 Walden Way, Paw Paw, MI 49079 (US). **BARBACHYN, Michael, R.** [US/US]; 2900 Redbud Trail, Kalamazoo, MI 49009 (US). **HESTER, Jackson, B., Jr.** [US/US]; 9219 East ML Avenue, Galesburg, MI 49053 (US). **JOHNSON, Paul, D.** [US/US]; 7060 S. 10th Street, Kalamazoo, MI 49009 (US). **CISKE, Fred, L.** [US/US]; 26431 Riesling Summit, Lawton, MI 49065 (US).

(74) Agent: **YANG, Lucy, X.**; Global Intellectual Property, Pharmacia & Upjohn Company, 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

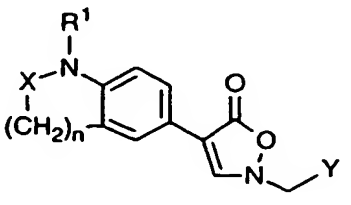
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/102785 A1

(54) Title: NOVEL BICYCLIC ISOXAZOLINONES AS ANTIBACTERIAL AGENTS



(I)

(57) Abstract: The present invention provides compounds of formula I useful as antimicrobial agents wherein X, Y, R^1, and n are as defined in thereof.

NOVEL BICYCLIC ISOXAZOLINONES AS ANTIBACTERIAL AGENTS

BACKGROUND OF THE INVENTION

The present invention relates to novel bicyclic isoxazolinones compounds and their preparations. These compounds are useful against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiply-resistant staphylococci and streptococci, anaerobic organisms such as bacteroides and clostridia species, and acid-fast organisms such as *Mycobacterium tuberculosis* and *Mycobacterium avium*.

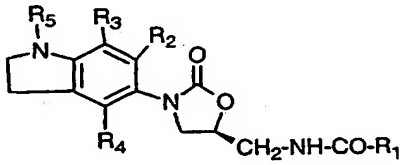
INFORMATION DISCLOSURE

PCT publications, WO 99/64416, WO99/64417, and WO 00/21960 disclose isoxazolinone derivatives useful as antibacterial agents.

PCT publication, WO 00/10566 discloses isoxazolinones useful as antibacterial agents.

US Patent application 09/57216 discloses novel bicyclic isoxazolinones as antibacterial agnets.

US Patent No. 5,164,510 discloses 5'-indolinyloxazolidin-2-ones of formula XI



XI

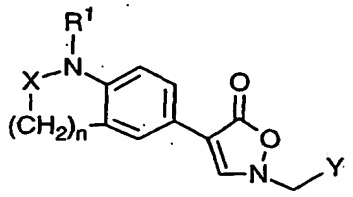
which are useful as antibacterial agents.

US Patent Nos. 5,036,092; 5,036,093; 5,039,690; 5,032,605 and 4,965,268 disclose aminomethyl oxazolidinyl aza cycloalkylbenzene derivatives useful as antibacterial agents.

US Patent Nos. 5,792,765 and 5,684,023 disclose substituted isoxazolinones useful as antibacterial agents.

SUMMARY OF THE INVENTION

The present invention provides a compound of formula I



I

or a pharmaceutically acceptable salt thereof wherein

Y is

a) $-NHC(=W)R^2$, or

b) -O-het, -S-het, or –NH-het;

W is

a) O, or

b) S;

X is

a) $-S(=O)_m-$, or

b) $-CHR^3-$;

R^1 is

a) C_{1-8} alkyl,

b) $-C(=O)R^4$, or

c) $-C(=S)NHC_{1-4}$ alkyl;

R^2 is

a) H,

b) C_{1-6} alkyl,

c) cyclopropyl,

d) $-OC_{1-4}$ alkyl,

e) $-NH_2$,

f) $-NHC_{1-6}$ alkyl, or

g) $-N(C_{1-6}\text{ alkyl})_2$;

R^3 is H, or C_{1-4} alkyl;

R^4 is

a) H,

b) C_{1-6} alkyl,

c) $-CH_2OC(=O)C_{1-4}$ alkyl;

at each occurrence above, alkyl is optionally substituted with one or more R^5;

R^5 is

a) halo,

b) CN,

c) NO_2,

d) C_{1-6} alkyl,

e) phenyl,

f) OR^6,

g) $C(=O)R^6$,

h) $OC(=O)R^6$,

i) $C(=O)OR^6$,

j) $S(=O)_mR^6$,

k) $S(=O)_mNR^6R^6$,

l) $NHC(=O)R^6$,

m) $C(=O)NR^6R^6$,

n) NR^6R^6,

R^6 is independently H, C_{1-6}alkyl, phenyl, or het;

het is a C-linked five- (5) or six- (6) membered saturated or unsaturated heterocyclic ring having 1, 2, or 3 heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen, which is optionally fused to a benzene ring; wherein het is optionally substituted with one or more halo, CN, NO_2, C_{1-6} alkyl, OR^6, phenyl, $S(=O)_mR^6$, $C(=O)R^6$, $OC(=O)R^6$, $NHC(=O)R^6$, or NR^6R^6, oxo, or oxime;

m is 0, 1 or 2; and n is 1 or 2.

In another aspect, the present invention also provides:

a pharmaceutical composition comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient (the composition preferably comprises a therapeutically effective amount of the compound or salt),

a method for treating gram-positive microbial infections in humans or other warm-blooded animals by administering to the subject in need a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof,

a method for treating gram-negative microbial infections in humans or other warm-blooded animals by administering to the subject in need a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

The invention also provides some novel intermediates and processes disclosed herein that are useful for preparing compounds of formula I.

DETAILED DESCRIPTION OF THE INVENTION

The following definitions are used, unless otherwise described.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, C_{1-7} alkyl refers to alkyl of one to seven carbon atoms, inclusive.

The compounds of the present invention are generally named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill in the art may be used (e.g. "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "O" for oxygen atom, "S" for sulfur atom, "N" for nitrogen atom, "h" for hour or hours and "rt" for room temperature).

It will be appreciated by those skilled in the art that compounds of the present invention may have a or more chiral centers and be isolated in optically active or racemic form. The present invention encompasses any racemic, optically-active (such as enantiomers, diastereomers), tautomeric, or stereoisomeric form, or mixture thereof, of a compound of the invention.

The term halo refers to fluoro, chloro, bromo, or iodo.

The term alkyl refers to both straight and branched groups, but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to.

The term "het" refers to a five- (5) or six- (6) membered saturated or unsaturated heterocyclic ring having 1, 2, or 3 heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen, which is optionally fused to a benzene ring.

Examples of unsaturated "het" include pyridine, thiophene, furan, pyrazoline, pyrimidine, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazinyl, 4-oxo-2-imidazolyl, 2-imidazolyl, 4-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 4-oxo-2-oxazolyl, 5-oxazolyl, 1,2,3-oxathiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazole, 4-isothiazole, 5-isothiazole, 2-indolyl,
3-indolyl, 3-indazolyl, 2-benzoxazolyl, 2-benzothiazolyl, 2-benzimidazolyl, 2-benzofuranyl, 3-benzofuranyl, benzoisothiazole, benzisoxazole, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 3-isopyrrolyl, 4-isopyrrolyl, 5-isopyrrolyl, 1,2,3,-oxathiazole-1-oxide, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 5-oxo-1,2,4-oxadiazol-3-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 3-oxo-1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-oxo-1,3,4-thiadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,2,3,4-tetrazol-5-yl, 5-oxazolyl, 3-isothiazolyl, 4-isothiazolyl and 5-isothiazolyl, 1,3,4,-oxadiazole, 4-oxo-2-thiazolinyl, or 5-methyl-1,3,4-thiadiazol-2-yl, thiazoledione, 1,2,3,4-thiatriazole, or 1,2,4-dithiazolone.

Examples of saturated "het" include piperdinyl, piperazinyl, morpholinyl, thiomorpholinyl, azetidinyl, pyrrolidinyl, hydantoin, oxathiolane, oxazolidine, dioxolane, or imidazolidine.

At each occurrence, het may be substituted with one or more group as defined in the summary of the invention or in claims.

Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

Specifically, C_{1-4} alkyl, C_{1-6} alkyl and C_{1-8} alkyl can be an alkyl group having one to four, one to six, or one to eight carbon atoms respectively such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and their isomeric forms thereof;

A specific value for Y is $-NHC(=W)R^2$.

A specific value for W is oxygen atom.

A specific value for W is sulfur atom

A specific value for R^2 is alkyl.

A specific value for R^2 is methyl.

A specific value for R^2 is ethyl, dichloromethyl, dichloroethyl, or NH_2.

A specific value for R^1 is 2-fluoroethyl, glycolyl, methoxyacetyl, oxoethylacetate, or methylaminocarbothioyl.

A specific value for R^1 is formyl, oracetyl.

A specific value for X is $-CHR^3-$, wherein R^3 is H or C_{1-4}alkyl.

A specific value for X is $-SO_2-$.

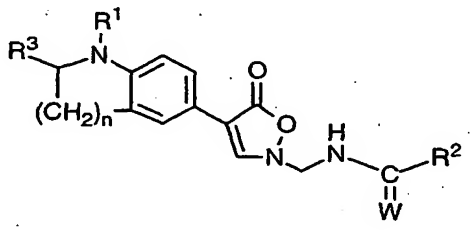
A specific value for Y is –O-het, –S-het, –NH-het.

A specific value for het is isoxazol-3-yl, isoxazol-5-yl, 1,2,4-oxadiazol-3-yl, isothiazol-3-yl, 1,2,4-thiadiazol-3-yl or 1,2,5-thiadiazol-3-yl.

A specific value for n is 1.

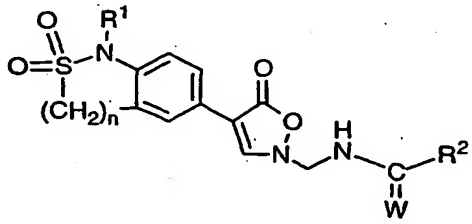
A specific value for n is 2.

A preferred compound of the present invention is a compound of formula IA:



IA.

Another preferred compound of the present invention is a compound of formula IB:



IB.

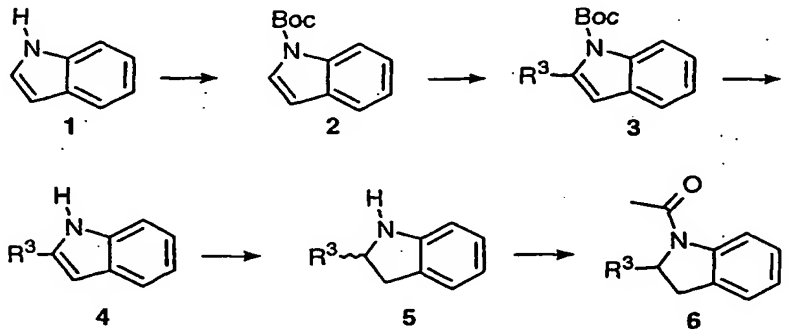
The following Charts I-V describe the preparation of compounds of the present invention. All of the starting materials are prepared by procedures described in these schemes or by procedures that would be well known to one of ordinary skill in organic chemistry. The variables used in the Schemes are as defined below or as in the claims. The compounds of this invention can be prepared in accordance to one or more of the processes discussed below.

INDOLINES

As shown in Chart I, the requisite 2-alkylindolines (n = 1) can be prepared from indole **1** or in the case of the methyl derivative **5** (R^3=CH_3) purchased from a commercial source. t-Butoxycarbonyl (Boc) protection of the indole nitrogen of **1** using di-t-

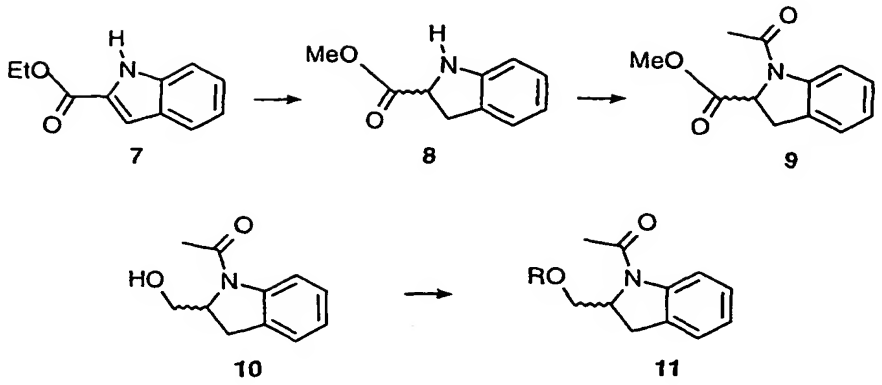
butyldicarbonate and catalytic dimethylaminopyridine (DMAP) followed by regioselective metalation with n-butyllithium, sec-butyllithium or tert-butyllithium and alkylation with an appropriate electrophile such as alkyl bromides and iodides gives N-Boc-2-alkylindoles **3** (R^3 is an alkyl group). Removal of the boc-protecting group affords 2-alkylindoles **4**. Reduction with sodiumcyanoborohydride will give the racemic indolines **5**. These can be acylated with acetic anhydride under well known conditions to provide the key indoline intermediates **6**.

CHART I



In addition, where other groups besides alkyl are desired at the 2-position of the indoline, one can start with commercially available ethyl indole-2-carboxylate **7** (Chart II). Reduction of **7** to the indoline intermediate **8** can be accomplished according to the procedure of Young et.al. (Tetrahedron Lett. **1986**, *27*, 2409-2410) with magnesium in methanol. Protection of the nitrogen by reaction with acetic anhydride will give **9**. Reduction of the ester to the alcohol **10** with an appropriate base such as lithium aluminumhydride, sodium borohydride or di-iso-butylaluminum hydride in a solvent such as diethyl ether or tetrahydrofuran or methanol can then be done at temperatures ranging from –78 - 60°C. Protection of the hydroxyl group with an appropriate protecting group such as a silyl ether provides indolines **11** (R = Si-(t-Bu)Me_2 or $SiMe_3$).

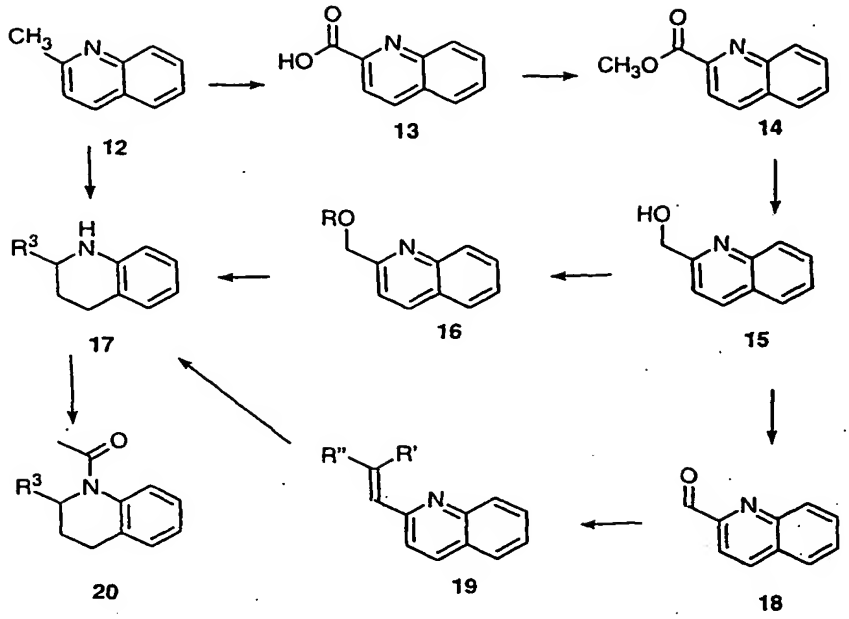
CHART II



TETRAHYDROQUINOLINES

Chart III illustrates the synthesis of requisite 2-substituted-tetrahydroquinoline intermediates **20**. The desired materials may be prepared from the commercially available quinaldine **12**. Oxidation of **12** to the acid **13** can be done according to the procedure of Campbell et al. (J. Am. Chem. Soc. **1946**, *68*, 1840). Conversion of the acid to the methyl ester in refluxing methanol with catalytic toluenesulfonic acid will give **14**. Reduction of the ester to corresponding alcohol **15** with an appropriate reducing agent (sodium borhohydride, lithium aluminumhydride) followed by the protection of the alcohol with a group such as a silyl ether will give **16** (R = Si-(t-Bu)Me_2 or $SiMe_3$). The alcohol **15** can also be converted to the aldehyde **18** via Swern oxidation. Olefination (Wittig reaction) of the aldehyde provides alkenes of type **19** (R' = alkyl or H, R'' = alkyl or H). Hydrogenation of materials **12, 16** or **19** in the presence of platinum oxide provides the requisite 2-substituted-tetrahydroquinolines **17** (R = alkyl, CH_2OSi-(t-Bu)Me_2 or CH_2OSiMe_3) as racemic mixtures. These tetrahydroquinolines can be acylated with acetic anhydride to give the requisite intermediates **20**.

CHART III



BICYCLIC ISOXAZOLINONES

The preparation of the final compounds is outlined in chart IV. The intermediates **6, 11,** and **20** can be acylated under Freidel Crafts conditions with acetyl chloride and aluminum chloride in carbon disulfide to provide intermediates **21** (n = 1 or 2). Treatment of these materials with thallium (III) nitrate trihydrate and 70% perchloric acid in methanol will yield the esters **22**. The N-acetyl group is then replaced with the t-butoxycarbonyl (Boc) protecting group by first refluxing **22** in 6N HCl and methanol to remove the acetate. The intermediate amine is then treated with di-t-butyldicarbonate and triethylamine in dichloromethane to give the Boc-protected esters **23**. Treatment of these materials with sodium hydride in ethylformate will yield the formylated derivatives **24**. The isoxazolinone rings can be prepared by treating **24** with aqueous hydroxylamine in methanol. The solvent can be stripped off in vacuo and the residue treated with N-(hydroxymethyl)acetamide acetate in dichloromethane with a suitable base such as potassium carbonate. This process yields the intermediates **25** (n = 1 or 2, R = alkyl, CH_2OSi-(t-Bu)Me_2 or CH_2OSiMe_3), R^2 = CH_3). The requisite N-(hydroxymethyl)acetamide acetate is prepared as described by WO 0010566 (2000). For example as shown in Chart IV, a compund of formula A (acetamide when $R^2 = CH_3$) can be reacted with 30-40% formaldehyde solution in water at temperatures ranging from 50-100 °C to give the N-hydroxymethyl acetamide **B** ($R^2 = CH_3$).

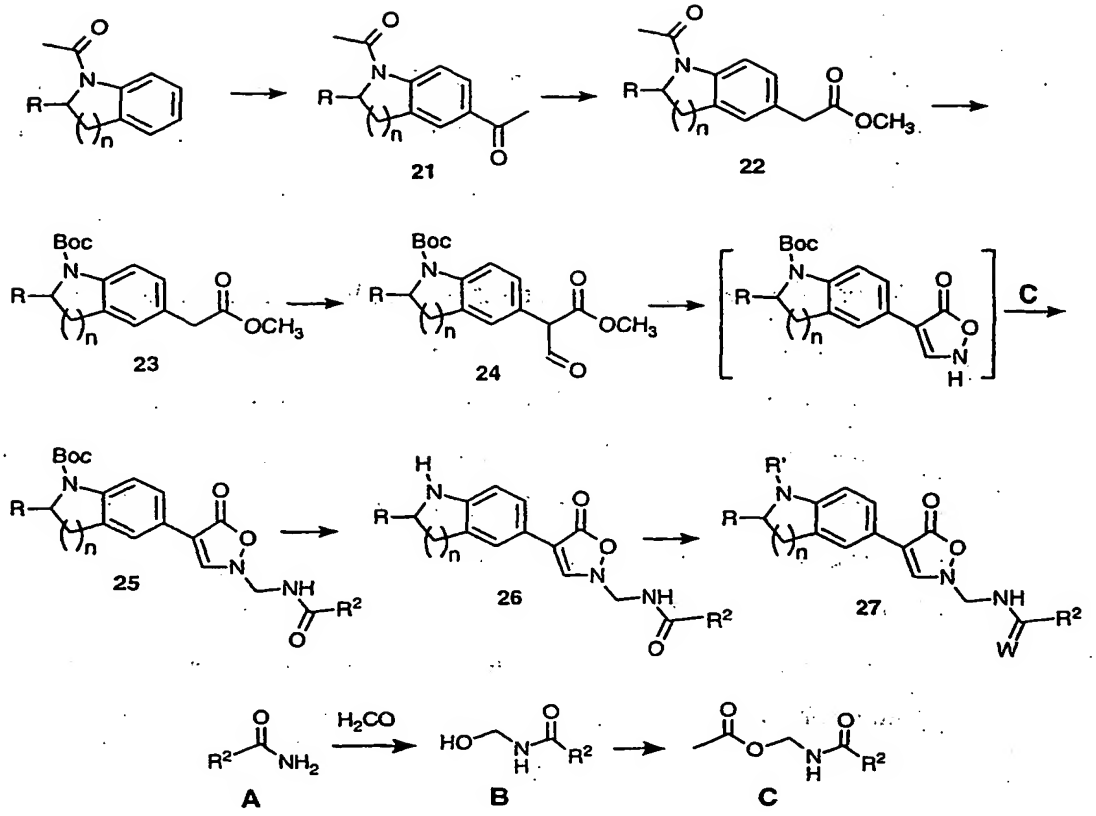
The structure **B** can be acylated with acetic anhydride with catalytic pyridine to yield the desired reagent **C** ($R^2 = CH_3$). Where other groups such as R^2 is C_{2-6}alkyl, cycloalkyl, O-alkyl, or NHalkyl are desired one skilled in the art can start with different primary carboxamides, carbamates or ureas **A** (R^2 = alkyl, O-alkyl, or NH-alkyl) as shown in Chart IV to give various reagents **C** (R = alkyl, O-alkyl, or NH-alkyl). The starting materials **A** may be purchased or prepared via methods well known to those skilled in the art.

The Boc-protecting group **25** can then be removed under acidic conditions (trifluoroacetic acid in dichloromethane or HCl(g) in dioxane) to yield the free amino derivatives **26**. The nitrogen can then be functionalized by a variety of well known methods to yield the desired analogs. For example, the deprotected materials can be acylated by reactions well known to those skilled in the art to give isoxazolones of structural formula **27** (R' = acyl, W = O). It can also be seen that other acyl derivatives, such as carbamates, can be prepared under similar conditions. In addition, the deprotected materials can be alkylated with alkyl halides and in the presence of appropriate bases (sodium hydride, triethyl amine, potassium carbonate) in a variety of solvents (dimethylformamide, tetrahydrofuran, acetone) to give isoxazolones of structural formula **27** (R' = alkyl, W = O).

Where other substitution on the 2-position of the indoline is desired, the protected alcohol derivatives **25** (R = CH_2OSi-(t-Bu)Me_2 or CH_2OSiMe_3) can be deprotected with flouride ion (eg, tetrabutylammonium fluoride). The resulting alcohols **25** (R= CH_2OH) can be alkylated with alkyl halides to prepare other ether derivatives **25** (R = CH_2O-alkyl) or acylated to give esters **25** (R = CH_2O-acyl). Alternatively, they can be activated as sulfonates (R = $CH_2OSO_2CH_3$) and displaced with amine nucleophiles to yield aminomethyl derivatives **25** (R = CH_2NH_2 or CH_2NHalkyl) which can be acylated, sulfonylated and/or alkylated to give **25** (R = CH_2NHCHO, CH_2NHCOalkyl, CH_2NHSO_2alkyl) by chemical methods well known to those trained in the art. Finally, such alcohols may be converted to the fluoro derivative **25** (R = CH_2F) via treatment with (diethylamino)sulfur trifluoride. These materials **25** can be converted to the products **27** (W = O) as described above.

The thioamides **27** (W = S) can be prepared by treating **27** (W = O) with Lawesson's reagent in tetrahydrofuran, dioxane or toluene at temperatures ranging from 50-110 °C.

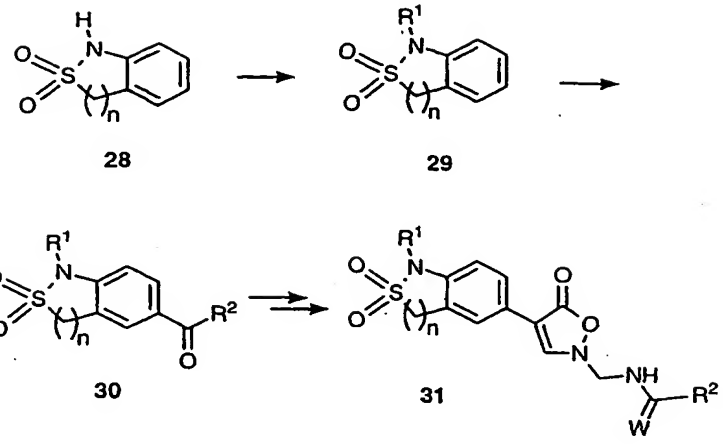
CHART IV



As shown in Chart V, sultam **28** (n = 1), obtained as per the method of Contri and Chiarino (J. Het. Chem. **1986,** *23,* 1645), is first converted to a sodium salt by treatment with a suitable base such as sodium bicarbonate. The nitrogen at the 1-position can then be alkylated by treatment with a variety of alkylating agents including alkyl halides and heating in a suitable solvent such as DMF. The intermediates **29** can then be acylated under Friedel-Crafts conditions (polyphosphoric acid in acetic anhydride at 80-110°C) to afford the ketones **30** (Skorez et al. *J. Het. Chem.* **1973,** *10,* 249.). These ketones can be transformed to the desired isoxazolinones **31** in an analogous manner to that outlined in Chart IV.

The benzosultam analogs where n = 2 can be prepared from the known intermediate **28** (n = 2) in the same fashion as described above (Sianesi, E. et al. *Chem. Ber.* **1971,** *104,* 1880).

CHART V



These compounds are useful for the treatment of microbial infections, including ophthalmologic infections, in humans and other warm blooded animals, under both parental and oral administration.

The pharmaceutical compositions of this invention may be prepared by combining the compounds of Formula I of this invention with a solid or liquid pharmaceutically acceptable carrier and, optionally, with pharmaceutically acceptable adjuvants and excipient employing standard and conventional techniques. Solid form compositions include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be at least one substance which may also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Inert solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, cellulosic materials, low melting wax, cocoa butter, and the like. Liquid form compositions include solutions, suspensions and emulsions. For example, there may be provided solutions of the compounds of this invention dissolved in water and water-propylene glycol and water-polyethylene glycol systems, optionally containing suitable conventional coloring agents, flavoring agents, stabilizers and thickening agents.

Preferably, the pharmaceutical composition is provided employing conventional techniques in unit dosage form containing effective or appropriate amounts of the active component, that is, the compounds of formula I according to this invention.

The quantity of active component, that is the compound of formula I according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the potency of the

particular compound and the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

In therapeutic use for treating, or combating, bacterial infections in warm-blooded animals, the compounds or pharmaceutical compositions thereof will be administered orally, topically, transdermally, and/or parenterally at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which will be antibacterially effective. Generally, such antibacterially effective amount of dosage of active component will be in the range of about 0.1 to about 100, more preferably about 3.0 to about 50 mg/kg of body weight/day. It is to be understood that the dosages may vary depending upon the requirements of the patient, the severity of the bacterial infection being treated, and the particular compound being used. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g., two to four times per day.

The compounds of formula I according to this invention are administered parenterally, i.e., by injection, for example, by intravenous injection or by other parenteral routes of administration. Pharmaceutical compositions for parenteral administration will generally contain a pharmaceutically acceptable amount of the compound according to formula I as a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as, for example, water-for-injection and a buffer to provide a suitably buffered isotonic solution, for example, having a pH of about 3.5-6. Suitable buffering agents include, for example, trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine to name but a few representative buffering agents. The compounds according to formula I generally will be dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 mg/ml to about 400 mg/ml of solution. The resulting liquid pharmaceutical composition will be administered so as to obtain the above-mentioned antibacterially effective amount of dosage. The compounds of formula I according to this invention are advantageously administered orally in solid and liquid dosage forms.

The isoxazolinone antibacterial agents of this invention have useful activity against a variety of organisms. The in vitro activity of compounds of this invention can be assessed by standard testing procedures such as the determination of minimum inhibitory concentration (MIC) by agar dilution as described in "Approved Standard. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically", 3rd. ed., published 1993 by the National Committee for Clinical Laboratory Standards, Villanova, Pennsylvania, USA. The activity of compounds of this invention against *Staphylococcus aureus*, is shown in Table 1.

TABLE 1

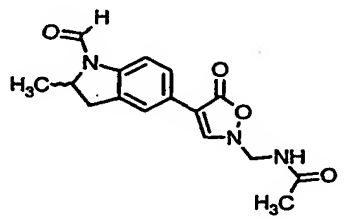
Antibacterial Activity, Minimum Inhibitory Concentration (μg/mL)

EXAMPLE #	S.A.
1	2
vancomycin	1

S.A is Methicillin-susceptible *S. aureus* UC®9213.

Minimum inhibitory concentration refers to lowest concentration of drug (μg/mL) that inhibits visible growth of the organism.

Example 1 N-{[4-(N-formyl-2-methylindolinyl)-5-oxo-isoxazol-2-yl]methyl}acetamide



Step 1 Preparation of N-acetyl-2-methylindoline

To a mixture of 2-methylindoline (20.0 g, 0.15 mol) and dimethylaminopyridine (500 mg, 5 mmol) in pyridine (50 mL) at room temperature is added acetic anhydride (20 mL). The mixture is stirred at ambient temperature for 18 h, diluted with ethyl acetate, washed with 1 N aqueous hydrochloric acid, water and brine, then dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give 26.3 g (100 %) of the title compound as an amber oil. MS (ESI+) *m/z* 176.1 (M+H).

Step 2 Preparation of N-acetyl-2-methylindolin-5-yl ethanone

To a mixture of the compound from Step 1 (2.0 g, 11.4 mmol) and aluminum chloride (7.0 g, 52 mmol) in carbon disulfide (20 mL) is added acetyl chloride (1.2 mL, 17.1 mmol). The mixture is heated at 50°C for 72 h, cooled, quenched with ice water then diluted with ethyl acetate and washed with water and brine, dried over anhydrous sodium sulfate, filtered, concentrated, and chromatographed on silica gel eluting with 40-50% ethyl acetate in heptane to give 2.4 g (97%) of the title compound as a off-white solid. MS (ESI+) *m/z* 217.1 (M+H). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.78; H, 6.98; N, 6.43.

Step 3 Preparation of methyl N-acetyl-2-methylindolin-5-yl acetate

The title compound from Step 2 (2.5 g, 11.4 mmol) and thallium (III) nitrate trihydrate (3.4 g, 12.7 mmol) in methanol (50 mL) are treated with 70% perchloric acid (7.5 mL) and stirred 18 h at room temperature. The mixture is filtered through celite, concentrated in vacuo, diluted with water and extracted with dichloromethane. The organics are washed with water and brine, dried over anhydrous sodium sulfate, filtered, concentrated and chromatographed on silica gel eluting with 50% ethyl acetate in heptane to give 1.40 g (49%) of the title compound as yellow oil. MS (ESI+) *m/z* 248.1 (M+H).

Step 4 Preparation of methyl N-[(t-butyl)oxycarbonyl]-2-methylindolin-5-yl acetate.

The compound from Step 3 (1.35 g, 5.5 mmol) and 6 N aqueous hydrochloric acid in methanol (20 mL) are refluxed for 18 h, cooled, concentrated to remove the methanol and poured into saturated aqueous sodium bicarbonate, then extracted with dichloromethane, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting oil is dissolved in dichloromethane (20 mL) and treated with triethylamine (1.3 mL) and di-t-butyl dicarbonate (1.3 g, 6.0 mmol). After stirring 18 h at room temperature the mixture is washed with water and brine, dried over anhydrous sodium sulfate, filtered, concentrated, and chromatographed on silica gel eluting with 15% ethyl acetate in heptane to give 1.04 g, (62%) of the title compound as a colorless oil. MS (ESI+) *m/z* 306.1 (M+H).

Step 5 Preparation of ethyl N-[(t-butyl)oxycarbonyl]-α-formyl-2-methylindolin-5-yl acetate.

60% sodium hydride in oil (550 mg, 13 mmol) is added at room temperature to a solution of the compound from Step 4 (1.00 g, 3.3 mmol) in ethyl formate (20 mL). The mixture is stirred at ambient temperature for 3 h, quenched with water, extracted with

dichloromethane, which is then dried over anhydrous sodium sulfate, filtered, concentrated, and chromatographed on silica gel eluting with 20% ethyl acetate in heptane to give 830 mg (73%) of the title compound as a yellow oil. MS (ESI+) *m/z* 348.1 (M+H).

Step 6 Preparation of N-[4-({N-[(t-butyl)oxycarbonyl]-2-methylindolin-5-yl}-5-oxo-isoxazolinyl)methyl]acetamide.

The compound form Step 5 (700 mg, 2.0 mmol) in methanol (20 mL) is treated with 50% aqueous hydroxylamine (1.4 mL, 20 mmol), stirred at room temperature for 3 h, then concentrated in vacuo. This residue is suspended in dichloromethane (20 mL) and treated with potassium carbonate (1.5 g, 11 mmol) and N-(hydroxymethyl)acetamide acetate (1.4 g, 10.6 mmol). The mixture is stirred at room temperature 18 h, poured into water, extracted with dichloromethane, dried over anhydrous sodium sulfate, filtered, concentrated, and chromatographed on silica gel eluting with 5% methanol in dichloromethane to give 360 mg (46%) of the title compound as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1 H), 7.5 (m, 2 H), 7.03 (t, J = 7.0 Hz, 1 H), 5.07 (d, J = 7.0 Hz, 2 H), 4.53 (bs, 1 H), 3.38 (dd, J = 10.3, 18.0 Hz, 1 H), 2.64 (d, J = 16.0 Hz, 1 H), 2.00 (s, 2 H), 1.58 (s, 9 H), 1.30 (d, J = 7.0 Hz, 3 H); MS (ESI-) *m/z* 422.0 (M+HCl). HRMS (FAB) calcd for $C_{20}H_{25}N_3O_5$+H_1 388.1872, found 388.1875.

Step 7 Preparation of N-[4-(2-methylindolinyl-5-oxo-isoxazolin-5-yl)methyl]acetamide.

To a solution of the compound from Step 6 (65 mg, 0.17 mmol) in dichloromethane (3 mL) is added trifluoroacetic acid (1 mL). The solution is stirred at room temperature for 2 h, washed with saturated aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate, filtered, concentrated in vauo to give 43 mg (89%) of the title compound as a brown solid. MS (ESI+) *m/z* 288.1 (M+H). HRMS (FAB) calcd for $C_{15}H_{17}N_3O_3$+H_1 288.1348, found 288.1351.

Step 8 Preparation of N-{[4-(N-formyl-2-methylindolin-5-yl)-5-oxo-isoxazol-2-yl]methyl}acetamide.

Acetic anhydride (50 µL) and 100% formic acid (40 µL) are heated at 50°C for 1 h under nitrogen, cooled to room temperature, diluted with THF (1 mL) and then treated with the compound from Step 7 (36 mg, 0.12 mmol) in THF (2 mL). The solution is stirred for 5 h, washed with water and brine, dried over anhydrous sodium sulfate, filtered, concentrated,

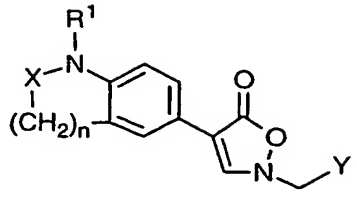
and chromatographed on silica gel eluting with 5% methanol in dichloromethane to give 25 mg (64%) of the title compound as an off-white solid. MS (ESI+) *m/z* 316.0 (M+H). HRMS (FAB) calcd for $C_{16}H_{17}N_3O_4+H_1$ 316.1297, found 316.1306.

5

CLAIMS

We claim:

1. A compound of formula I



I

or a pharmaceutically acceptable salt thereof wherein

Y is

a) -NHC(=W)R^2, or

b) -O-het, -S-het, or –NH-het;

W is

a) O, or

b) S;

X is

a) -S(=O)$_m$-, or

b) -CHR^3–;

R^1 is

a) C_{1-8} alkyl,

b) -C(=O)R^4, or

c) -C(=S)NHC_{1-4} alkyl;

R^2 is

a) H,

b) C_{1-6} alkyl,

c) cyclopropyl,

d) -OC_{1-4} alkyl,

e) $-NH_2$,

f) -NHC_{1-6} alkyl, or

g) -N(C_{1-6} alkyl)$_2$;

R^3 is H, or C_{1-4} alkyl;

R^4 is

a) H,

b) C_{1-6} alkyl,

c) $-CH_2OC(=O)C_{1-4}$ alkyl;

at each occurrence above, alkyl is optionally substituted with one or more R^5;

R^5 is

a) halo,

b) CN,

c) NO_2,

d) C_{1-6} alkyl,

e) phenyl,

f) OR^6,

g) $C(=O)R^6$,

h) $OC(=O)R^6$,

i) $C(=O)OR^6$,

j) $S(=O)_mR^6$,

k) $S(=O)_mNR^6R^6$,

l) $NHC(=O)R^6$,

m) $C(=O)NR^6R^6$,

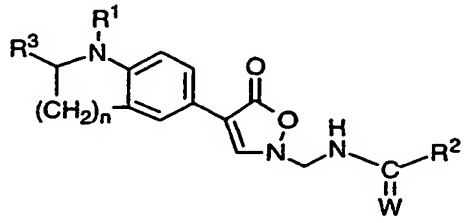
n) NR^6R^6,

R^6 is independently H, C_{1-6}alkyl, phenyl, or het;

het is a C-linked five- (5) or six- (6) membered saturated or unsaturated heterocyclic ring having 1, 2, or 3 heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen, which is optionally fused to a benzene ring; wherein het is optionally substituted with one or more halo, CN, NO_2, C_{1-6} alkyl, OR^6, phenyl, $S(=O)_mR^6$, $C(=O)R^6$, $OC(=O)R^6$, $NHC(=O)R^6$, or NR^6R^6, oxo, or oxime;

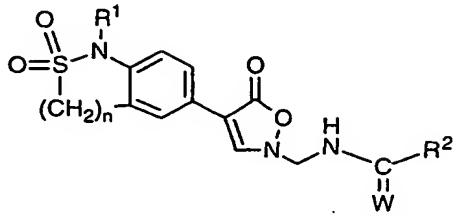
m is 0, 1 or 2; and n is 1 or 2.

2. A compound of claim 1 which is a compound of formula IA



IA.

3. A compound of claim 1 which is a compound of formula IB



IB.

4. A compound of claim 2 or 3 wherin R^2 is C_{1-6}alkyl.

5. A compound of claim 2 or 3 wherin R^2 is methyl.

6. A compound of claim 2 or 3 wherein R^1 is formyl or acetyl.

7. A compound of claim 2 or 3 wherein n is 1.

8. A compound of claim 2 or 3 wherein n is 2.

9. A compound of claim 2 or 3 wherein R^1 is 2-fluoroethyl, glycolyl, methoxyacetyl, oxoethylacetate, or methylaminocarbothioyl.

10. A compound of claim 2, wherein R^3 is methy.

11. A compound of claim 1 which N-{[4-(N-formyl-2-methylindolinyl)-5-oxo-isoxazol-2-yl]methyl}acetamide.

12. A compound of claim 1 where in het is isoxazol-3-yl, isoxazol-5-yl, 1,2,4-oxadiazol-3-yl, isothiazol-3-yl, 1,2,4-thiadiazol-3-yl or 1,2,5-thiadiazol-3-yl.

13. A use of a compound of claim 1 for manufacturing of a medicament for medical treatment of microbial infections in a mammal in need thereof.

14. The use of claim 13 wherein said compound of formula I is administered orally, parenterally, transdermally, or topically in a pharmaceutical composition.

15. The use of claim 13 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.

16. The use of claim 13 wherein said compound is administered in an amount of from about 1 to about 50 mg/kg of body weight/day.

17. A use for treating microbial infections of claim 13 wherein the infection is skin infection.

18. A use for treating microbial infections of claim 13 wherein the infection is eye infection.

19. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Internat(Application No
PCT/US 01/42943

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D261/12 C07D413/04 A61K31/42 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 164 510 A (BRICKNER STEVEN J) 17 November 1992 (1992-11-17) cited in the application column 49 -column 50; claims; examples	1-19
Y	WO 00 10566 A (SQUIBB BRISTOL MYERS CO) 2 March 2000 (2000-03-02) cited in the application claims; examples	1-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 November 2002	15/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Menegaki, F

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/42943

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18,19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat Application No
PCT/US 01/42943

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5164510 A	17-11-1992	US 5182403 A	26-01-1993
		US 5225565 A	06-07-1993
		AT 112773 T	15-10-1994
		AT 201870 T	15-06-2001
		AU 617871 B2	05-12-1991
		AU 4195789 A	02-04-1990
		CA 1335103 A1	04-04-1995
		DE 68918792 D1	17-11-1994
		DE 68929303 D1	12-07-2001
		DE 68929303 T2	02-05-2002
		DK 45591 A	13-03-1991
		EP 0359418 A1	21-03-1990
		EP 0434714 A1	03-07-1991
		EP 0609905 A1	10-08-1994
		ES 2157934 T3	01-09-2001
		GR 3036491 T3	30-11-2001
		HK 1002234 A1	07-08-1998
		JP 3188418 B2	16-07-2001
		JP 11080139 A	26-03-1999
		JP 2865211 B2	08-03-1999
		JP 4500665 T	06-02-1992
		KR 138262 B1	15-05-1998
		WO 9002744 A1	22-03-1990
WO 0010566 A	02-03-2000	AU 748750 B2	13-06-2002
		AU 5783399 A	14-03-2000
		BR 9913225 A	22-05-2001
		CA 2341271 A1	02-03-2000
		CN 1314813 T	26-09-2001
		CZ 20010669 A3	15-08-2001
		EP 1107756 A1	20-06-2001
		HU 0103433 A2	28-01-2002
		JP 2002523369 T	30-07-2002
		NO 20010916 A	10-04-2001
		PL 346267 A1	28-01-2002
		TR 200100672 T2	23-07-2001
		WO 0010566 A1	02-03-2000
		US 6420349 B1	16-07-2002
		US 2002094984 A1	18-07-2002